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PATENT COVER SHEET FOR PROVISIONAL APPLICATION

Transmitted herewith for filing under 37 CFR §1.53(c) is the PROVISIONAL APPLICATION for patent of

INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
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TITLE OF THE INVENTION (280 characters max)

USE OF ORGANIC COMPOUNDS

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ENCLOSED APPLICATION PARTS *(check all that apply)*

- ☒ Specification (Including Any Claims and Abstract) - 8 pages
- ☐ Drawings - sheets
- ☒ Other (specify): Application Data Sheet

METHOD OF PAYMENT

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☐ U.S. Government agency and contract number: (if the invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.)

Respectfully submitted,

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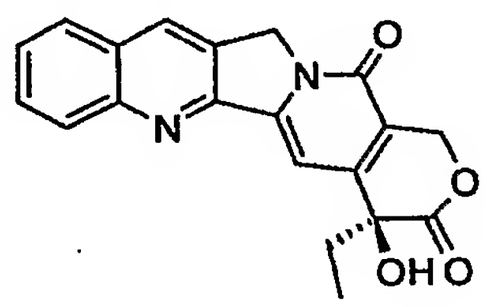
Case 4-33648P1/PROV/USN

Use of Organic Compounds

The invention relates to a pharmaceutical combination which comprises (a) a topoisomerase I inhibitor compound and (b) a compound (IAP inhibitor) that inhibits the caspase-9 inhibiting properties of an inhibitor of apoptosis protein (IAP) and optionally at least one pharmaceutically acceptable carrier for simultaneous, separate or sequential use, in particular for the delay of progression or treatment of a proliferative disease, especially a solid tumor disease; a pharmaceutical composition comprising such a combination; the use of such a combination for the preparation of a medicament for the delay of progression or treatment of a proliferative disease; a commercial package or product comprising such a combination as a combined preparation for simultaneous, separate or sequential use; and to a method of treatment of a warm-blooded animal, especially a human. A greater than additive effect is seen when compounds (a) and (b) are used in combination.

DNA topoisomerases are enzymes essential for the relaxation of DNA during a number of critical processes, including replication, transcription, and repair. There are two types of topoisomerases; topoisomerase I and topoisomerase II. Camptothecin and related compounds are the most important inhibitors of topoisomerase I.

Camptothecin is a plant alkaloid of the following structure



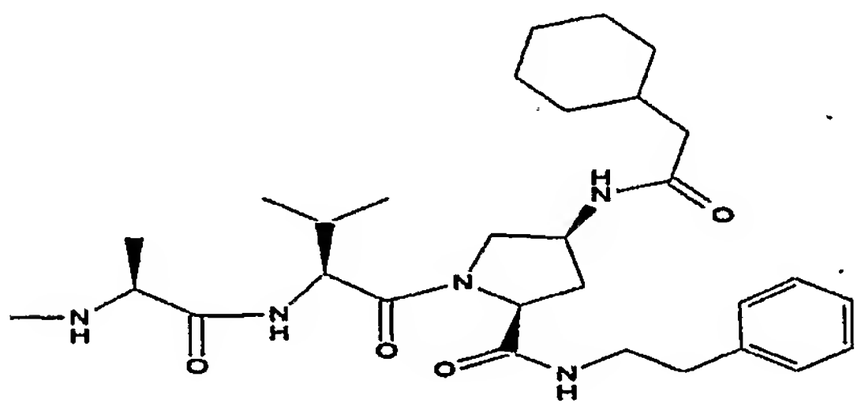
Irinotecan and topotecan are related compounds that are approved for treatment of certain cancers. In addition, several topoisomerase I inhibitors that are structurally related to camptothecin are in development, including BNP1350, SN38, 9-amino-camptothecin, lurtotecan, gimatecan, several homocamptothecins, such as diflomotecan, and several conjugates, usually via the 20S hydroxy or a 10 hydroxy, with, for example,

carboxymethyldextran, poly-L-gutamic acid, polyethylene glycol and the like, such as T-0128, DX-310, CT-2106 and Protecan.

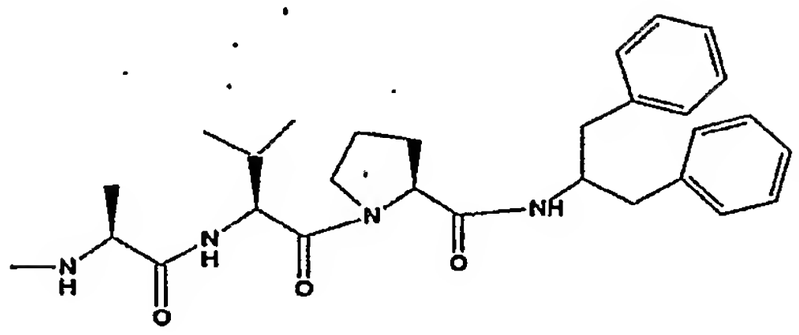
A recently reported molecular mechanism for circumvention of apoptosis involves the overexpression of members of the IAP family. IAPs sabotage apoptosis by directly interacting with and neutralizing Caspases. The prototype IAP, XIAP, has three functional domains referred to as BIR 1, 2 & 3 domains. BIR3 interacts directly with Caspase 9 and inhibits its ability to bind and cleave its natural substrate, Procaspase 3. Thus, in an important embodiment of this invention, IAP inhibitor compound inhibits the interaction between the BIR3 domain of XIAP and Caspase-9.

Therepeutic compounds that inhibit the interaction between the BIR3 domain of XIAP and Caspase-9 include mimetics of SMAC and antisense nucleic acids, for example as claimed in U.S. Patent No. 6,300,492.

Mimetics of SMAC include compounds described in WO2004/005248, in particular compound C



or compound D:



Hence, the present invention also pertains to a combination such as a combined preparation or a pharmaceutical composition which comprises (a) a topoisomerase I inhibitor and (b) an IAP inhibitor.

The term "a combined preparation", as used herein defines especially a "kit of parts" in the sense that the combination partners (a) and (b) as defined above can be dosed independently or by use of different fixed combinations with distinguished amounts of the combination partners (a) and (b), i.e., simultaneously or at different time points. The parts of the kit of parts can then, e.g., be administered simultaneously or chronologically staggered, that is at different time points and with equal or different time intervals for any part of the kit of parts. The ratio of the total amounts of the combination partner (a) to the combination partner (b) to be administered in the combined preparation can be varied, e.g. in order to cope with the needs of a patient sub-population to be treated or the needs of the single.

The present invention especially relates to a combined preparation, which comprises (a) one or more unit dosage forms of topoisomerase I inhibitor and (b) one or more unit dosage forms of an IAP inhibitor.

The term "delay of progression" as used herein means administration of the combination to patients being in a pre-stage or in an early phase of the proliferative disease to be treated, in which patients for example a pre-form of the corresponding disease is diagnosed or which patients are in a condition, e.g. during a medical treatment or a condition resulting from an accident, under which it is likely that a corresponding disease will develop.

The term "solid tumor" especially means breast cancer, ovarian cancer, cancer of the colon and generally the GI tract, cervix cancer, lung cancer, in particular small-cell lung cancer, and non-small-cell lung cancer, head and neck cancer, bladder cancer, cancer of the prostate or Kaposi's sarcoma. The present combination inhibits the growth of solid tumors, but also liquid tumors. Furthermore, depending on the tumor type and the particular combination used a decrease of the tumor volume can be obtained. The combinations disclosed herein are also suited to prevent the metastatic spread of tumors and the growth or development of micrometastases. The combinations disclosed herein are in particular suitable for the treatment of poor prognosis patients, especially such poor prognosis patients having non-small-cell lung cancer.

It will be understood that references to the combination partners (a) and (b) are meant to also include the pharmaceutically acceptable salts. If these combination partners (a) and (b) have, for example, at least one basic center, they can form acid addition salts. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The combination partners (a) and (b) having an acid group (for example COOH) can also form salts with bases. The combination partner (a) or (b) or a pharmaceutically acceptable salt thereof may also be used in form of a hydrate or include other solvents used for crystallization.

A combination which comprises (a) a topoisomerase I inhibitor and (b) an IAP inhibitor, in which the active ingredients are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier, will be referred to hereinafter as a COMBINATION OF THE INVENTION.

It is one objective of this invention to provide a pharmaceutical composition comprising a quantity, which is therapeutically effective against a proliferative disease comprising the COMBINATION OF THE INVENTION. In this composition, the combination partners (a) and (b) can be administered together, one after the other or separately in one combined unit dosage form or in two separate unit dosage forms. The unit dosage form may also be a fixed combination.

The pharmaceutical compositions according to the invention can be prepared in a manner known per se and are those suitable for enteral, such as oral or rectal, and parenteral administration to mammals (warm-blooded animals), including man. Alternatively, when the agents are administered separately, one can be an enteral formulation and the other can be administered parenterally.

The novel pharmaceutical composition contain, for example, from about 10 % to about 100 %, preferably from about 20 % to about 60 %, of the active ingredients. Pharmaceutical preparations for the combination therapy for enteral or parenteral administration are, for example, those in unit dosage forms, such as sugar-coated tablets, tablets, capsules or suppositories, and furthermore ampoules. If not indicated otherwise, these are prepared in a manner known per se, for example by means of conventional mixing, granulating, sugar-coating, dissolving or lyophilizing processes. It will be appreciated that the unit content of a combination partner contained in an individual dose of each dosage form need not in itself constitute an effective amount since the necessary effective amount can be reached by administration of a plurality of dosage units.

In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents; or carriers such as starches, sugars, microcristalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, capsules and tablets, with the solid oral preparations being preferred over the liquid preparations. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed.

In particular, a therapeutically effective amount of each of the combination partner of the COMBINATION OF THE INVENTION may be administered simultaneously or sequentially and in any order, and the components may be administered separately or as a fixed combination. For example, the method of delay of progression or treatment of a proliferative disease according to the invention may comprise (i) administration of the first combination partner in

free or pharmaceutically acceptable salt form and (ii) adminstration of the second combination partner in free or pharmaceutically acceptable salt form, simultaneously or sequentially in any order, in jointly therapeutically effective amounts, preferably in synergistically effective amounts. The individual combination partners of the COMBINATION OF THE INVENTION can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. Furthermore, the term administering also encompasses the use of a pro-drug of a combination partner that convert *in vivo* to the combination partner as such. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

The effective dosage of each of the combination partners employed in the COMBINATION OF THE INVENTION may vary depending on the particular compound or pharmaceutical composition employed, the mode of administration, the condition being treated, the severity of the condition being treated. Thus, the dosage regimen the COMBINATION OF THE INVENTION is selected in accordance with a variety of factors including the route of administration and the renal and hepatic function of the patient. A physician, clinician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the single active ingredients required to prevent, counter or arrest the progress of the condition. Optimal precision in achieving concentration of the epothilone derivative within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the active ingredients' availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of the active ingredients.

The COMBINATION OF THE INVENTION can be a combined preparation or a pharmaceutical composition.

Moreover, the present invention relates to a method of treating a warm-blooded animal having a proliferative disease comprising administering to the animal a COMBINATION OF THE INVENTION in a quantity which is therapeutically effective against a proliferative disease and which reduces any diarrhea associated with the administration of the epothilone derivative.

Furthermore, the present invention pertains to the use of a COMBINATION OF THE INVENTION for the delay of progression or treatment of a proliferative disease and for the preparation of a medicament for the delay of progression or treatment of a proliferative disease.

Moreover, the present invention provides a commercial package comprising as active ingredients COMBINATION OF THE INVENTION, together with instructions for simultaneous, separate or sequential use thereof in the delay of progression or treatment of a proliferative disease.

The following Examples illustrate the invention described above; they are not, however, intended to limit the scope of the invention in any way. The beneficial effects of the COMBINATION OF THE INVENTION can also be determined by other test models known as such to the person skilled in the pertinent art.

Example 1: In a melanoma model, compound D (250 nM) shows growth at about 90% of control, camptothecin (5 nM) shows growth of about 50% of control while the combination of compound D (250 nM) and camptothecin (5 nM) shows growth of less than 3% of control.

Example 2: In a breast tumor model, both compound C and topotecan (1 nM) individually increase caspase-3 activity less than two fold over the control. A nearly twelve fold increase in caspase-3 activity is seen with the same amount of compound C at a concentration of about 1 nM topotecan.

What is claimed is:

1. A method of treating a proliferative disease in a patient; which comprises administering to the patient an effective combination of (a) a topoisomease I inhibitor and (b) an IAP inibitor.

2. A combined preparation, which comprises (a) one or more unit dosage forms of topoisomerase I inhibitor and (b) one or more unit dosage forms of an IAP inhibitor.